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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/647,278	09/26/2000	Janet M. Hock	X-11965	5427

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EXAMINER	
LI, RUIXIANG	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/647,278	HOCK, JANET M.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/31/2003, 11/18/2003, and 01/12/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35 and 65-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35 and 65-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/31/03 & 1/12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendment and Claims

The Request on October 31, 2003 for Continued Examination (RCE) under 37 CFR 1.114 of Application 09/647,278 is granted. An action on the RCE follows.

Applicants' amendments, which were filed on October 31, 2003, November 18, 2003, and January 12, 2004, have been entered in full. Claims 67 and 68 have been added. Claims 35 and 65-68 are currently pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Information Disclosure Statement

All the references listed in PTO-1449 except the one that is numbered as "Can" have been considered by the Examiner because the information of the reference is incomplete (the date is missing).

Withdrawn Objections and/or Rejections

As indicated in the Advisory Action of July 23, 2003, on entering Applicants' amendment filed on July 3, 2003, claims 59-63 were canceled, and the rejection of claims 59-63 set forth in the office Action of April 30, 2003 was thus made moot. The objection of claim

35 for minor informalities has also been withdrawn in view of Applicants' amendment to the claim.

Claim Rejection Under 35 U. S. C. § 102 (b)/103(a)

In view of Applicants' amendment to the claims and for the purpose of clarity, a new rejection is set forth below to replace the rejection under 35 U. S. C. § 102 (b) of the record.

(i) The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(ii) The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(iii) This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

(iv) Claims 35 and 65-68 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Neer et al. (U.S. Patent No. 4,698,328, October 1987).

Neer et al. teach a method for the treatment of osteoporosis in human subject to increase bone mass, comprising administering human PTH (1-34) in combination with various forms of vitamin D or a dietary calcium supplement (Abstract; column 5-6; claims 1-15), or in combination with both vitamin D and a dietary calcium supplement (column 3, lines 44-54). Neer et al. teach that the method of treatment is intended to be used in all diseases classified as osteoporosis, such as postmenopausal osteoporosis, senile osteoporosis, osteoporosis secondary to gonadal insufficiency, or osteoporosis that is a sequella of hyperparathyroidism or glucocorticoid excess (bottom of column 3).

Neer et al. teach ranges of administration of hPTH1-34 at a daily dose of 100-700 units (top of column 5). Neer et al. teach 'units' are defined in terms of the International Reference Preparation of hPTH1-34 and expressed in the chick hypercalcemic assay. Neer et al. further teach that the ranges of administration are those high enough to stimulate bone remodeling in humans, yet not so high as to produce net bone resorption nor enough bone mineral mobilization to produce hypercalcemia or hypercalciuria (top of column 5).

Claims 35 and 65-68 require the limitation of a daily dose of 20 μg hPTH1-34. The reference of Neer et al. teach a daily dose of 100-700 units, but does not specifically mention the daily dose of 20 μg as claimed. As evidenced by the prosecution to date, including prior art, there is no art-accepted conversion of units to μg for hPTH1-34. However, also for the reasons of record, the PTO concludes that the claimed daily dose of 20 μg to be consistent with the prior art.

For example, Zanelli et al. (World Health Organization, Parathyroid Hormone, bovine, for Bioassay, 1985) teach a research standard of hPTH1-34 (82/508), 8.61 units/μg (unweighted geometric mean potency estimate), which was determined with various in vitro and in vivo assays by various laboratories (Tables 1 & 8). This biological potency was in close agreement with the original estimate of 10 units/μg based on the chick hypercalcaemia bioassay (top of page 5 and Table 1). Zanelli et al. further recommended that the preparation of hPTH 1-34 should be made available as calibrated standards for international distribution, pending the availability of more highly purified materials as candidate international standard (middle of page 6). Based upon the conversion factor, 8.61 units/μg, taught by Zanelli et al., the daily dosage of 100-700 units would be 11.6-81 μg/day, which covers the daily dosage of 20 μg claimed in the instant invention.

Finkelstein et al. (JAMA, 280:1067-1073, 1998) and Finkelstein et al. (N Engl J Med, 331:1618-1623, 1994) teach that 40 μg =500 units (12.5 units/μg) and the bioassay

used to determine the activity of hPTH (1-34). This would convert the daily dose of 100-700 units to 8-56 μg. It is noted that both papers include Neer as an author. Other references also teach the conversion factor. Based upon the calculation that 400 units =25 μg (used in the previous office action in Paper No. 9; source: Lindsay 1997, 1993, IDS codes CB and CD; Lane 1998, IDS code, CE), 100-700 units/day is equivalent to 6.3-43.8 μg/day. If the average conversion factor (which was obtained by averaging all the specific activity values provided by the Applicants on page 19 of Applicants' response filed on 2/14/2003), 10.8 units/μg, is used, 100-700 units/day is equivalent to 9.2-64.8 μg/day. Therefore, the reference of Neer et al. appears to meet the limitations of claims 35 and 65-68.

With these conditions, where the method seems to be identical except that the prior art is silent to the characteristic dosage claimed, then the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Note the case law of In re Best 195 USPQ 430, 433 (CCPA 1977).

Applicants' Argument

In Applicants' responses filed on October 31, 2003 and January 12, 2004, Applicants continue to argue (i) that Neer et al. do not teach the hPTH1-34 daily dose of 20 μg, do not provide the basis to convert the units to μg, the activity of PTH is quite sensitive to the particular assay used, as supported by Applicants' prior declaration; (ii) that the rejection imported specific activity value into Neer et al. from secondary prior art references that go beyond merely explaining what was contained in Neer et al; (iii) the

rejection rests on uncertain results; (iv) the prior art does not teach or suggest reduction fracture by hPTH1-34 treatment.

Applicants' arguments have been fully considered, but are not deemed to be persuasive for the following reasons. First, Neer et al. teach a method for the treatment of osteoporosis in human subject, comprising administering human PTH (1-34) at a daily dose of 100-700 units. Neer et al. teach 'units' are defined in terms of the International Reference Preparation of hPTH1-34 and expressed in the chick hypercalcemic assay. Thus, based upon the teachings of Neer et al., an artisan can readily convert the daily dose of 100-700 units to μg by searching the art or by simply performing the chick hypercalcemic assay to determine the conversion factor from units to μg, as noted above. The Examiner's position that the daily dosage in units can be readily converted to the daily dosage in ug is further supported by the following fact: the article of Neer et al. (N Engl J Med 344:1434-1441, 2001; post filing date of the instant application) teach the use of the daily dosage of 20 ug PTH (1-34) for treatment of osteoporosis and reduction of bone fracture in postmenopausal woman with osteoporosis.

Second, the activity of the same hPTH1-34 preparation is measurable and can be determined. The measurements using various in vitro and in vivo assays, including the chick hypercalcemic assay, are in close agreement, as demonstrated by Zanelli et al. (World Health Organization, Parathyroid Hormone, bovine, for Bioassay, 1985). Zanelli et al. teach a research standard of hPTH1-34 (82/508), 8.61 units/μg (unweighted geometric mean potency estimate), which was determined with various in vitro and in

vivo assays by various laboratories (Tables 1 & 8). This biological potency was in close agreement with the original estimate of 10 units/μg based on the chick hypercalcaemia bioassay (top of page 5 and Table 1). This is in sharp contrast to Applicants argument and declaration that the activity of PTH is quite sensitive to the particular assay used.

Third, Neer et al. provide specific, sufficient guidance on how to administer an appropriate amount of the hPTH1-34: the ranges of administration are those high enough to stimulate bone remodeling in humans, yet not so high as to produce net bone resorption nor enough bone mineral mobilization to produce hypercalcemia or hypercalciuria (top of column 5). Thus, an artisan would be able to adjust the dose of hPTH1-34 in patients with osteoporosis even variation of the hPTH1-34 activity (units/μg) exists.

Finally, it is noted that the term "osteoporosis" is defined as "reduction in the quantity of bone or atrophy of skeletal tissue; an age-related disorder characterized by decreased bone mass and increased susceptibility to fractures" (Stedman's Medical Dictionary 27th Edition). Thus, since Neer et al. teach treatment of osteoporosis with hPTH1-34, Neer et al. inherently teach reducing the risk of bone fracture. The Examiner's position is evidenced by the prior art of record. For example, Lindsay et al. (The Lancet, 350:550-555, 1997) teach that treatment of postmenopausal women with osteoporosis with hPTH (1-34) in a daily dosage of 25 ug increased total-body bone mineral and that the increased vertebral mass was associated with a reduced rate of vertebral fracture. Lindsay et al. further teach that bone-mass chages may be consistent with a reduction

in all osteoporotic fractures (page 550, right column). Cosman et al. teach that hPTH (1-34) increases bone mass and perhaps a reduction in osteoporotic fracture (Abstract). Hirano et al. teach that hPTH (1-34) enhances the mechanical strength of cortical bone in rabbits (abstract). Furthermore, Turner et al. teach hPTH (1-34) induces parallel increases in bone mass and bone strength in animals, which is clearly cited in the the article of N Engl J Med 344:1434-1441, 2001. One of the inventors, Gregory A. Gaich, is also a co-author of the article.

Accordingly, the reference of Neer et al. appears to meet the limitations of claims 35 and 65-68 and the rejection of claims under 35 U.S.C. 102(b)/103(a) is required.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday-Friday, 8:30 am-5:00 pm.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and

should be addressed to [yvonne.eyler@uspto.gov]. All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Ruixiang Li
Examiner
February 19, 2004

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER